REMARKS

Claims 1-25 and 35-71 are the pending claims. Claims 70 and 71 are newly added. Support for new claims 70 and 71 may be found in the specification as originally filed, for example, at pages 18 and 23. Claims 45, and 48 are amended for clarity to more positively recite the method steps. Support for the other amendments to claims 45 and 48 may be found in the specification as originally filed, for example, pages 13 and 16-17.

I. Applicants' Claim to Priority

The Examiner has acknowledged Applicants' claims to priority. The first line of the specification has been amended to add the patent number of the parent application.

II. The Information Disclosure Statement

The Examiner has crossed off three Japanese language references cited on the PTO Form 1449 attached to the Office Action, apparently signaling that the Examiner has not considered the references.

Applicants respectfully submit that the Examiner should consider the three crossed off Japanese language references. Said references were properly cited and considered in the parent application. The USPTO rules require that the Examiner should consider all of the references cited in the parent application. See MPEP 609.03. Therefore, Applicants respectfully request consideration of all of the cited references.

For the convenience of the Examiner, enclosed herewith is the International Search Report, which was submitted in the parent application as part of the "concise statement of relevance" for non-English language documents.

III. The Objection to the Abstract

The abstract of the disclosure was objected to as being more than one paragraph in length.

Serial No. 10/716,430

The abstract has been amended and rewritten to one paragraph in length. It is respectfully submitted that Applicant's abstract fully complies with 37 C.F.R. §1.72(b) and MPEP §608.01(b) and it is requested that the objection to the Abstract be reconsidered and withdrawn.

IV. The Rejections Under 35 U.S.C. §112

Claims 45-49 and 69 rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite.

The Examiner request that "R1" be amended with "precise definition." The Examiner also request that claim 69 be amended to include the structural formulae (1) and (2).

Applicants respectfully submit that the present claims are clear and definite as written and that they particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, second paragraph, in view of the following remarks.

Claim 69 has been cancelled.

As to the definition for "R¹", to advance prosecution, "R¹" and "R²" have been amended to represent a hydrogen atom or an alkyl or an aralkyl group which is capable of serving as an ester type protective group of a carboxyl group. This is the change approved by the Examiner in the earlier proposed Examiner's amendment.

For the above reasons, it is respectfully submitted that Applicants' claims are clear and definite and it is requested that the rejection under 35 U.S.C. §112 be reconsidered and withdrawn.

V. The Rejection Under 35 U.S.C. §102

Claim 69 is rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Mita et al, "Method for Preparation of Aziridine-2-Carboxylic Acid Salts" (JP 57-146751).

Claim 69 has been cancelled. Therefore, the rejection of claim 69 is moot.

VI. The Rejection Under 35 U.S.C. §103

Claims 45-49 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Mita et al.

The Examiner's position is that the Examples of Mita et al disclose each step in claim 45, except for specific temperature. The Examiner notes that Mita et al generically discloses a temperature range of 0 to 100 °C.

As to claim 48, the Examiner notes that the examples of Mita et al use sodium hydroxide, potassium hydroxide or calcium hydroxide as the base. The Examiner also notes Mita et al discloses that the base can be ammonia water. The Examiner alleges that amines are organic derivates of ammonia in the same way that alcohols and ethers are organic derivates of water and concludes that the use of amines or ammonia water is not a patentably distinct difference.

Applicants respectfully submit that the present invention is not anticipated by or obvious over the disclosures of Mita et al and request that the Examiner reconsider and withdraw this rejection in view of the following remarks.

Independent claims 45 and 48 recite a process for producing an optically active aziridine-2-carboxylic acid derivative ... comprising ... performing an intramolecular cyclization reaction on an optically active 3-haloalanine derivative ... Mita et al simply does not teach or disclose the use of an optically active 3-haloalanine derivative to produce an optically active N-protected-aziridine-2-carboxylic acid. Mita et al describes a process for producing a racemic 3-haloalanine derivative under the presence of a base and Mita et al discloses the use of an intramolecular cyclization reaction. However, Mita et al discloses nothing about a process for producing an optically active 3-haloalanine derivative at all. The Examiner has not set forth or even mentioned why one skilled in the art, in view of Mita et al, would use an optically active 3-haloalanine derivative to produce an optically active N-protected-aziridine-2-carboxylic acid.

The Examiner has not made a *prima facie* case of obviousness in view of Mita et al and the obviousness rejection based on Mita et al should be withdrawn for that reason alone.

While, as set forth above, it is believed the Examiner has not established a *prima facie* case of obviousness, to advance the prosecution of the case, the following discussion shows how Applicants' claimed methods provide unexpectedly improved properties over the disclosures of Mita et al.

Concerning claims 45-47 and 70-71:

Example 1 of Mita et al uses a racemic chloroalanine as a raw material. The chloroalanine is a hydrochloric acid salt of chloroalanine. Reference Example 1 of Applicants' specification is similar to Example 1 of Mita et al, except that, instead of racemic chloroalanine, optically active (S)-chloroalanine is used as a raw material. Additionally, because Reference Example 1 uses chloroalanine instead of the hydrochloric acid salt of chloroalanine as a raw material, a reduced amount of sodium hydroxide is used by the amount considered to be consumed by hydrochloric acid. (The equivalence of the base used for aziridination is the same as in Example 1 of Mita et al.).

The yield of (S)-aziridine-2-carboxylic acid in Reference Example 1 is 29%, which is markedly lower than those of Examples 1, 5 and 8 of the present application where NaOH is used as the base. As is described in Applicants' specification, (S)-aziridine-2-carboxylic acid is obtained with a low yield if the reaction is conducted at 25 to 60°C. Thus, Applicants' invention of claim 45 involves more than just switching from a racemic to an optically raw material. Comparing Reference Example 1 to Example 1 of Mita et al shows that Compound (2) cannot be obtained at a high yield only by making the raw material an optically active one.

Similarly, Reference Example 2 of the present specification is similar to Example 2 of Mita et al. Example 2 of Mita et al uses racemic chloroalanine and Reference Example 2 uses optically active (S)-

¹ See pages 85-88 of Applicants' specification for the Reference Example. The other examples are on pages 61-85.

chloroalanine is used as a raw material. Again, due to the use of chloroalanine instead of the hydrochloric acid salt of chloroalanine as a raw material, a reduced amount of sodium hydroxide is used (The equivalence of the base used for aziridination is the same as in Example 2 of Mita et al.).

Reference Example 2 shows a yield of (S)-aziridine-2-carboxylic acid is 13%. Again, it is clear that (S)-aziridine-2-carboxylic acid cannot be obtained at a high yield by carrying out the method set forth in Mita et al. by only the replacement of the raw material to an optically active one. Moreover, by comparing Examples 1 and 3, and Reference Example 3 of the present invention, it is seen that the yield unexpected improves with a reaction temperature of 70°C or higher.

The base used in Example 6 of Applicants' specification, Mg(OH)₂, is different than those of the specific examples of Mita et al (NaOH, KOH and Ca(OH)₂). Therefore, Example 6 is not listed in the Table below as not being directly representative of specific examples shown Mita et al. The yield of Example 6 is 42%.

Further, since optically active aziridine compound is unstable at elevated temperatures, decomposition or racemization is predicted. Thus, in the case where literature disclosing the reaction of the racemic compound, as in Mita et al, those skilled in the art would expect that a reaction at a lower temperature should be used in order to efficiently cause the reaction. However, it is unexpected that the reaction in the present invention can achieve a high yield at an elevated temperature as high as 70°C or higher.

Accordingly, one skilled in the art would not have predicted that the yield of optically active aziridine-2-carboxylic acid remarkably improves at a temperature of 70°C or higher, as set forth in claim 45 of the present invention. Applicants respectfully submit that the present invention is unobvious and that the present invention is not a simple optimization of the reaction temperature.

Amendment Under 37 CFR 1.111 Serial No. 10/716,430

Table: Compa	arison of the Exam	iples from Applicants' Specif	Scation with	Examples of Mita et al.				
		Substrate Base Base/substrate (eq)	Base	Base/substrate (eq)	Temp.	Reaction	Yield	Stereo
				(used for		time	8	Configuration of
				aziridination reaction)				the Product
Example 1	Inventive	(S)-Chloroalanine	NaOH	2	06	10 min.	87	(S)-form
Example 5	Inventive	(S)-Chloroalanine	NaOH	2	70	0.5 hr.	81	(S)-form
Reference Example 3	Comparative (Only to claim 45)	(S)-Chloroalanine	NaOH	2	20	1 hr.	53	(S)-form
Reference Example 1	Comparative (Only to claim 45)	(S)-Chloroalanine	NaOH	2.2	25	24 hr.	29	(S)-form
Mita et al	Comparative	Chloroalanine HCl salt	NaOH	2.2	Room	24 hr.	97.6	Racemic mixture
Example 1		(racemic: Mixture of (S) and (R) Chloroalanine HCl			Temp.			of (S) and (R)- forms
Reference Example 2	Comparative (Only to claim 45)	(S)-Chloroalanine	КОН	2.2	09	4 hr.	13	(S)-form
Mita et al	Comparative	Chloroalanine HCl salt	КОН	2.2	09	4 hr.	88.3	Racemic mixture
Example 2		(racemic: Mixture of (S) and (R) Chloroalanine HCl salt)	-					or (5) and (K)- forms
Example 8	Inventive	(S)-Chloroalanine methyl ester HCl salt	NaOH	2	06	10 min.	38	(S)-form
Mita et al Example 3	Comparative	Chloroalanine methyl ester HCl salt	NaOH	2.3	09	4 hr.	91.3	Racemic mixture of (S) and (R)-
		(racemic: Mixture of (S) and (R) Chloroalanine methyl ester HCl salt)						forms
Mita et al	Comparative	Chloroalanine HCl salt	Ca(OH) ₂	5	09	4 hr.	84.7	Racemic mixture
Example 4		(racemic: Mixture of (S) and (R) Chloroalanine HCl						of (S) and (R)- forms
		salt)						
Example 7	Inventive	(S)-Chloroalanine	Ca(OH) ₂	2	90	30 min.	47	(S)-form

Concerning claims 48 and 49:

As to claim 48, the Examiner notes Mita et al discloses that the base can be ammonia and water.

The Examiner alleges that amines are organic derivates of ammonia in the same way that alcohols and ethers are organic derivates of water and concludes that the use of amines or ammonia water is not a patentably distinct difference. The Examiner also states that "the difference between an amine and ammonia is slight," and that "one of ordinary skill in the art would recognize that ammonia, NH₄OH, is a derivative of amine," and the Examiner concludes that the use of an amine rather than ammonia would be obvious "to prepare a higher yield."

The Examiner cites Ex parte Bluestone, 135 USPQ 199 (1961) as support for his conclusion.

Again, Applicants' claims recite a process for producing an optically active aziridine-2-carboxylic acid derivative. Mita et al discloses nothing about a process for producing an optically active 3-haloalanine derivative at all. The Examiner has not set forth or even mentioned why one skilled in the art, in view of Mita et al, would use an optically active 3-haloalanine derivative to produce an optically active N-protected-aziridine-2-carboxylic acid. Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness in view of Mita et al and the obviousness rejection based on Mita et al should be withdrawn for that reason alone.

Further, in *Bluestone*, relied upon by the Examiner, the Board of Appeals held that the difference between secondary and tertiary amines was not a patentable difference. One reason for the Board's decision was that the applicant did not traverse the examiner's judicial notice of art-recognized equivalents. However, the Examiner's instant rejection does not even involve adjacent homologs (compounds differing by a -CH₂- group), as in *Bluestone*. For compounds that differ structurally by a -CH₂- group, unless their equivalency or close relationship would have been recognized by those skilled in the art, no showing is needed to establish patentability. *Ex parte Thompson*, 119 USPQ 254 (POBA

1954). Accord, *In re Shetty*, 195 USPQ 753 (CCPA 1977). The existence of an adjacent homolog to the claimed compound in the prior art does not conclusively establish *prima facie* obviousness. *In re Lalu*, 223 USPO 1257 (Fed. Cir. 1984).

In the present rejection, the Examiner has not established the equivalency or close relationship would have been recognized by those skilled in the art in the field of preparation of aziridine carboxylic acid salts. Further, the Examiner has not provided any support in the art for his statement that the use of an amine rather than ammonia would be obvious "to prepare a higher yield." Therefore, it is respectfully submitted that the Examiner has not established a *prima facie* case of obviousness

While, as set forth above, it is believed the Examiner has not established a *prima facie* case of obviousness, to advance the prosecution of the case, Applicants have provided additional declaration evidence showing the improved properties of the presently claimed process for producing an optically active N-protected-aziridine-2-carboxylic acid by performing an intramolecular cyclization reaction in the presence of an amine over a representative process for producing an optically active N-protected-aziridine-2-carboxylic acid by performing an intramolecular cyclization reaction in the presence of ammonia. See the Declaration Under 37 C.F.R. §1.132 filed concurrently herewith. Experimental Example 1 is closer in scope to the present invention than the teachings of Mita due to its performing an intramolecular cyclization reaction on an optically active 3-haloalanine derivative to produce an optically active N-protected-aziridine-2-carboxylic acid.

The 132 Declaration compares Examples 9-13 of the present specification, which use an amine as a base, with Experimental Example 1 of the 132 Declaration, which uses an aqueous ammonia. As can be seen from a comparison of the data, when an amine was used (as in claim 48) an extremely high yield was obtained. Further, the Declarant states that this difference is an unexpected effect. When an Applicant demonstrates substantially improved results and states that

Amendment Under 37 CFR 1.111

Serial No. 10/716,430

the results were unexpected, this should suffice to establish unexpected results in the absence of

evidence to the contrary. In re Soni, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995).

For the above reasons, it is respectfully submitted that the subject matter of claims 45-49 is

neither taught by nor made obvious from the disclosures of Mita et al and it is requested that the rejection

under 35 U.S.C. §103(a) be reconsidered and withdrawn.

VII. Conclusion

In view of the aforementioned amendments and accompanying remarks, Applicant submits that

that the pending claims are in condition for allowance. Applicant requests such action at an early date.

If this Amendment is not timely filed, Applicant respectfully petition for an appropriate

extension of time. The fees for such an extension or any other fees that may be due with respect to this

paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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Page 35